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Age-related differences in the neural correlates of trial-to-trial variations of reaction time

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ABSTRACT

Intra-subject variation in reaction time (ISVRT) is a developmentally-important phenomenon that decreases from childhood through young adulthood in parallel with the development of executive functions and networks. Prior work has shown a significant association between trial-by-trial variations in reaction time (RT) and trial-by-trial variations in brain activity as measured by the blood-oxygenated level-dependent (BOLD) response in functional magnetic resonance imaging (fMRI) studies. It remains unclear, however, whether such “RT-BOLD” relationships vary with age. Here, we determined whether such trial-by-trial relationships vary with age in a cross-sectional design. We observed an association between age and RT-BOLD relationships in 11 clusters located in visual/occipital regions, frontal and parietal association cortex, precentral/postcentral gyrus, and thalamus. Some of these relationships were negative, reflecting increased BOLD associated with decreased RT, manifesting around the time of stimulus presentation and positive several seconds later. Critically for present purposes, all RT-BOLD relationships increased with age. Thus, RT-BOLD relationships may reflect robust, measurable changes in the brain-behavior relationship across development.

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1. Introduction

Intra-subject variation in reaction time (ISVRT) is a measure of a subject's consistency in responding to stimuli across a task, often quantified as the standard deviation of RT across a task epoch; higher ISVRT, reflected in larger standard deviations, is associated with greater variability, or inconsistency, of responses. ISVRT is a

Abbreviations: ISVRT, Intra-subject variation in reaction time; RT-BOLD relationship, change in the Blood Oxygenation Level Dependent signal associated with 1 s increase in reaction time.

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developmentally-important phenomenon; it decreases from childhood through young adulthood (Williams et al., 2005, 2007; Dykiert et al., 2012; Li et al., 2009, 2004; Tamnes et al., 2012), paralleling the behavioral development of executive functions such as attention and self-regulation (Gomez-Guerrero et al., 2011), as well as structural brain development within the frontal lobes (Marsh et al., 2008; Giedd, 2004; Gogtay et al., 2004). Further, atypical ISVRT is associated with developmental disorders of executive control linked to atypical brain development (Bora et al., 2006; Leth-Steensen et al., 2000; Kaiser et al., 2008; Adleman et al., 2014, 2012; Brotman et al., 2009; Castellanos et al., 2005; Epstein et al., 2011). Thus, determining how the relationship between ISVRT and brain activity supporting executive functions varies with age may ultimately inform our understanding of both normal and atypical cognitive development.

To elucidate the development of neural mechanisms mediating age-related changes in behavior, it is important to map brain-behavior associations across age (Pfeifer and Allen, 2012). Poldrack has emphasized the importance of quantifying such associations precisely (Poldrack, 2014). However, most developmental studies examine the relationship between activation and neural responses

averaged over time (Poldrack, 2014), rather than at the level of specific trials. ISVRT is a particularly well-suited construct with which to delineate the development of brain-behavior associations in a precise fashion because 1) ISVRT has been shown to change with age, 2) RT varies at the level of specific trials, and 3) RT can be measured easily.

One approach to directly mapping brain-behavior relationships employs functional magnetic resonance imaging (fMRI) to link trial-specific changes in RT to trial-specific changes in the BOLD signal (Weissman et al., 2006). Using this approach in adults, several researchers have reported robust “RT-BOLD relationships” in frontal and parietal regions during executive function tasks (Weissman et al., 2006; Chee and Tan, 2010; Prado and Weissman, 2011; Yarkoni et al., 2009). Moreover, some researchers have reported that the size of the RT-BOLD relationship varies across populations who differ in their attentional abilities. For example, in frontal and parietal regions crucial for attention, stronger RT-BOLD relationships manifest in individuals who exhibit minimal, relative to marked, effects of sleep deprivation on attention (Chee and Tan, 2010; Chee et al., 2008). Similarly, investigating developmental differences in the RT-BOLD relationship may help to reveal which neural processes underlie developmental differences in executive functioning (Plude et al., 1994; Anderson et al., 2001; Rueda et al., 2004; Ridderinkhof and van der Stelt, 2000).

Along these lines, it is presently unclear whether children and adolescents show similar RT-BOLD relationships to adults. Carp and colleagues found weak or absent RT-BOLD associations in a relatively small sample of children and adolescents ($n=18$) as compared to a group of young adults ($n=21$) (Carp et al., 2012). Analogous to the above-noted findings on sleep deprivation, weaker RT-BOLD associations in children and adolescents compared to adults could reflect reduced attentional capacity early in development (Plude et al., 1994; Rueda et al., 2004; Ridderinkhof and van der Stelt, 2000). However, Kim and colleagues identified strong, linear RT-BOLD relationships in a larger ($n=28$) sample of children (Kim et al., 2013), thereby raising the possibility that the first study was underpowered. Further, neither study employed age as a continuous variable to investigate more specifically how the RT-BOLD relationship varies cross-sectionally with age. Finally, both studies modeled RT-BOLD relationships using a canonical hemodynamic response function, which precludes the ability to distinguish between RT-BOLD relationships that occur “early” versus “late” in the average time-locked BOLD response to a trial type. Nonetheless, these “early” and “late” relationships can be quite different, possibly in ways that relate to early lapses of attention and later compensatory effects (Weissman et al., 2006). For all of these reasons, it remains unclear whether and when in the course of a neural response the RT-BOLD relationship differs between children and adults.

The goal of the present study was to answer these questions using methods that characterize RT-BOLD relationships throughout the course of each trial during the performance of a selective attention task that requires the engagement of executive function (Weissman et al., 2006). To this end, we used a finite impulse response (FIR) model to derive empirically the average event-related BOLD response to target stimuli in a selective attention task (Ollinger et al., 2001). We then compared both “early” and “late” time points of the RT-BOLD relationship in healthy children and adults. Finally, we employed age as a continuous variable to investigate more specifically how the RT-BOLD relationship varies across development.

Finally, initial studies examining the relationship between ISVRT and brain activation correlated overall subject ISVRT measures with task-related average neural responses across individuals (e.g., Bellgrove et al., 2004). While these studies shed light on the overall relationship between a subject’s level of variability and

his/her brain activity as compared to other subjects, they could not isolate the relationships between RT variability and BOLD response at the level of a single trial. One of the first experiments to include a measure of RT as a regressor in fMRI analysis, and thus to examine parametric modulation of the BOLD response by RT was by Gilbert and colleagues (Gilbert et al., 2006). This study used $\log(\text{RT})$ during low-demand tasks as a regressor in the fMRI general linear model. Other studies have utilized mean and, in some cases, standard deviations of RTs to calculate and standardize individual trial RT either within (Yarkoni et al., 2009) or across (Hahn et al., 2007) subjects. These standardized trial RTs are included as regressors in the general linear model, often using a standard HRF function (e.g., Carp et al., 2012; Kim et al., 2013; Gilbert et al., 2006; Hahn et al., 2007). However, as stated by Yarkoni and colleagues (Yarkoni et al., 2009), differences in RT may not only be related to changes in the amplitude of the BOLD signal and thus, some studies utilize a FIR model to estimate the RT-BOLD relationship (Weissman et al., 2006; Yarkoni et al., 2009) to avoid making assumptions about its shape. The analysis in the present study was modeled after that of Weissman et al. (2006), and hence we employed similar techniques for RT standardization and modeling the RT-BOLD relationship. However, this study is the first to examine age differences in the RT-BOLD relationship using a FIR model and including age as a continuous variable.

2. Materials and methods

2.1. Participants

The protocol was approved by the National Institutes of Health Intramural Research Program Combined Neuroscience Institutional Review Board, which is accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. Fifty-seven individuals participated in the study. Data were excluded from seven: two individuals were excluded for excessive head motion during the fMRI scan (average motion per TR before censoring >0.25 mm or more than 8% of TRs censored for motion) and five individuals were excluded for poor task performance (accuracy below 70% on any single run). Thus, fifty healthy participants (33 female, 17 male), ranging in age from 9.5 to 42.9 years (mean: 21.9 ± 7.0), were included in the final analyses (see Supplemental Fig. 1 for age histogram). Written consent and assent were acquired before the experiment began. Semi-structured psychiatric interviews by trained clinicians confirmed that participants had no history of psychiatric illness or psychotropic medication use, and no first-degree relative with a mood or anxiety disorder. Participants were in good physical health as indicated by medical history and physical exam. Participants were excluded for $\text{IQ} < 70$ on the Wechsler Abbreviated Scale of Intelligence (Clements, 1965), history of substance abuse within 2 months, head trauma, neurological disorder, pervasive developmental disorder, or contraindications to MRI.

2.2. In-scanner behavioral paradigm

Participants performed a modified global-local selective attention task (Weissman et al., 2006) programmed in E-prime and projected onto a screen viewed via a mirror mounted on the head coil. There were four stimuli that appeared equally often. Each stimulus was a large letter (“H” or “S”) made up of several identical smaller letters (“Hs” or “Ss”; see Supplemental Fig. 2). Half the stimuli were congruent (e.g., a large H made up of small H) while the other half were incongruent (e.g., a large S made up of small Hs). All stimuli appeared centered on a red fixation point. Moreover, each stimulus appeared for 200 ms and was followed by 2300 ms of fixation.

In alternating runs, participants were asked to identify the large global letter (H or S) or the small local letters (Hs or Ss) that appeared in each trial. They did so by pressing one of two buttons on a two-button response device using either the left thumb or the right thumb. Stimulus presentation and jitter orders were created with AFNI's `make_random_timing.py` program. Thus, the maximum inter-stimulus interval varied across run orders, as optimized by this program. The inter-stimulus interval was jittered in units of the TR (1250 ms) and ranged from 2.5 s to 12.5–16.25 s (mean inter-stimulus interval: 3.98 s). Participants were pseudo-randomly assigned to one of 80 run orders selected from 10,000 iterations. We included six runs, each of which contained 96 trials: 48 congruent and 48 incongruent. At the end of each run, the overall number of correct responses, errors, and percent correct were displayed. Further details about the task and scan parameters are available in (Chen et al., 2014).

2.3. Imaging acquisition

Neuroimaging data were collected on a 3-T General Electric Signa scanner and 32-channel head coil. After acquisition of a sagittal localizer scan, an automated shim calibrated the magnetic field to reduce signal dropout due to susceptibility artifact. Six functional runs of 304 time points each were acquired using 24 contiguous 5-mm interleaved axial slices covering the entire brain. These scans used a 64×64 matrix with echoplanar single shot gradient echo T2* weighting (TR = 1250 ms; TE = 25 ms; FOV = 240 mm; flip angle = 35°), yielding $3.75 \times 3.75 \times 5$ mm voxels. To reach longitudinal magnetization equilibrium, the six initial images from each run were discarded. A high-resolution structural MPRAGE scan (1-mm interleaved sagittal slices; TE = min full; TI = 425; FOV = 25.6; freq x phase = 256×256 ; flip angle = 7° ; 1 mm^3 voxels) was also acquired during the same session for coregistration with the functional data. Because of the inhomogeneity introduced by a 32-channel head coil, an ASSET calibration scan followed by a proton-density weighted (PDW) scan with similar parameters to the MPRAGE scan were conducted immediately prior to acquisition of the structural scan, and the PDW scan was used to correct the MPRAGE before pre-processing steps were conducted (in 7 subjects, the uncorrected MPRAGE was used in pre-processing due lack of alignment between the PDW and MPRAGE).

2.4. Behavioral data analysis

Trials were considered errors if a response occurred in less than 100 ms from the onset on the stimulus, no response was made within 2500 ms, or the response was incorrect. Five participants whose accuracy fell below 70% for at least a single run were excluded. For the remaining 50 participants, we calculated mean reaction times for correct trials. As a behavioral measure of ISVRT, we used each participant's coefficient of variation of RT (standard deviation of RT divided by mean RT). We employed this measure because the mean and standard deviation of RT may be highly correlated (Wagenmakers and Brown, 2007). Nonparametric correlational analyses were run between age and the following measures: mean accuracy for all trials, mean RT for all trials and for each trial type independently, and coefficient of variation of RT across all trials and for each trial type independently.

2.5. Imaging analysis

Functional magnetic resonance imaging data were analyzed using Analysis of Functional NeuroImages (AFNI; <http://afni.nimh.nih.gov/afni/>; (Cox, 1996)) using standard preprocessing including slice-timing alignment, alignment of all volumes to base volume and registration to Talairach template, spatial smoothing (6-mm

FWHM kernel), masking, and intensity scaling. TRs n and $n+1$ were censored if the normed motion vector between time points was greater than 1 mm. Participants were excluded if the average motion per TR before censoring was >0.25 mm or if more than 8% of TRs were censored for motion. There was no correlation between age and average motion per TR before censoring (p 's > 0.44). Finally, motion parameters were included as covariates in the regression analysis.

Mean standardized RT was calculated for each trial by using the RT for that individual trial and subtracting from it that participant's mean RT value for that trial type (congruent or incongruent) in the same run (Weissman et al., 2006). Therefore, trial-specific mean-standardized RT gauged participant's RT for each individual trial, referenced to his or her overall performance in that condition: lower mean-standardized RT indicated faster relative RT and higher mean-standardized RT indicated slower relative RT.

To avoid prior assumptions about the expected BOLD response shape and to quantify precisely the chronometry of variation in the RT-BOLD relationship, we analyzed the fMRI data using a finite impulse response (FIR) linear regression model. Each trial was modeled with 13 basis functions (i.e., tents), each of which spanned 1 TR. In other words, each trial was modeled with a 13 TR (15 s) time window starting 2.5 s before stimulus onset and continuing for a total of 15 s (i.e., final tent at 12.5 s after stimulus onset), resulting in 13 regressors per stimulus type (i.e., condition).

For each condition (i.e., congruent, incongruent), we created 26 regressors as follows. First, we modeled the hemodynamic response associated with average RT across trials with 13 TENT basis functions (or linear splines) that capture the BOLD response over a period of 15 s with a TR of 1.25 s. In addition, to obtain the RT-modulated effect per condition, we used the de-meaned mean-standardized RT values at all the trials of the condition and then multiplied those 13 TENT basis functions, creating another 13 regressors (i.e., 13 TENT basis functions and 13 RT-modulated functions). The de-meaning step allowed us to obtain the response shape and magnitude through the first set of 13 basis functions. Finally, a third-order Legendre polynomial modeling baseline drift, incorrect trials, and 6 head motion parameters were included in each participant's model to control for potential confounding effects.

For each participant, two effects of interest were estimated for each trial type: 1) the average stimulus-locked BOLD response (i.e., the BOLD response across time associated with the average RT) and 2) the RT-BOLD relationship (i.e., the change in the BOLD response associated with a 1 s increase in RT, as measured by mean-standardized RT) (Weissman et al., 2006). The mean-standardized RT value for each trial was used to represent trial RT in order to control for differences in overall RT within a subject across trial types or blocks, or across subjects. Specifically, we estimated the following: the average BOLD response to congruent trials across 13 TRs (average congruent), the average BOLD response to incongruent trials across 13 TRs (average incongruent), the average RT-BOLD relationship for congruent trials across 13 TRs (RT-BOLD congruent), and the average RT-BOLD relationship for incongruent trials across 13 TRs (RT-BOLD incongruent).

2.5.1. Developmental changes in trial-to-trial RT-BOLD relationships

For all group analyses, we employed AFNI's 3dClustSim (using a 70% group mask and averaged error terms from all subjects) to calculate the cluster extent ($k = 38$) needed to obtain FWE-correction across the brain at $p < 0.05$ with an initial height threshold of $p < 0.005$.

For group analyses, beta estimates were entered into a multivariate model (Chen et al., 2014) using 3dMVM in AFNI. In these models, condition (congruent, incongruent) and tent (or TR,

referred to as time point from here on) served as within-participant variables while participant age served as a quantitative, **continuous** variable. Thus, no grouping by age was included in the model; instead, age was a continuous variable.

Separate models were created to examine the relationship between age as a continuous variable and 1) the average BOLD response regressors and 2) the RT-BOLD relationship regressors. The average response regressor analysis and results will not be discussed further (the results of this analysis are available in Supplemental information). Indeed, the model for the RT-BOLD relationship was of primary interest as it determines whether brain activity varies with trial-specific RT and, most importantly, *whether such RT-BOLD relationships are related to age*.

In clusters wherein a significant age \times time point (i.e., TR) interaction was revealed, percent signal change values for each condition \times time point combination were extracted separately for each participant. Since age was included as a continuous variable in the model, the significant interaction indicated that the RT-BOLD relationship varied across the full age distribution in the sample in these clusters. However, it did not indicate the direction of the relationship. Therefore, to visualize the direction of the relationship, we created “representative images.” These images, generated for display purposes only, averaged values in groups of subjects from specific age bands (see Fig. 1). While the RT-BOLD associations varied continuously across all ages, in these figures we depict the findings using three groups, each consisting of 16 subjects (this number was arbitrarily determined). These three groups were selected to represent RT-BOLD associations across the entire age range. Specifically, the first group included the sixteen youngest participants (youngest), the second was generated from sixteen subjects around the overall sample median age (middle), and the third included the sixteen oldest participants (oldest). The average RT-BOLD associations from each of these representative groups were plotted to illustrate the responses across all 13 time points (or TRs) in each significant cluster resulting from the multivariate models. Again, the model included age as a continuous variable and these graphs are for illustrative purposes only. Scatterplots of age by RT-BOLD relationship across all subjects in each significant TR in each of the regions in which there was a significant age \times time point interaction are available in Supplemental Fig. 5.

2.5.2. Presence of RT-BOLD relationships in children and adolescents

The results of our primary analyses indicated the presence of developmental differences in RT-BOLD relationships, which were driven by increasing RT-BOLD relationships with age. However, an absence of RT-BOLD associations in younger subjects might produce similar findings. Indeed, results from two previous studies of children and adolescents were contradictory about the presence of RT-BOLD associations in this population. The first study found weak RT-BOLD associations manifesting only in the lateral parietal cortex in children and adolescents (Carp et al., 2012). The second study (Kim et al., 2013) reported several regions with linear RT-BOLD relationships in a sample of children and adolescents, but did not directly compare this sample to an adult group (of note, this study only tested for positive RT-BOLD relationships).

To clarify these findings and our own, we conducted analyses designed to determine whether RT-BOLD relationships were indeed present and measurable in children and adolescents. First, we identified regions in which there was a main effect of time point (i.e., tent) in our overall group RT-BOLD analysis, indicating a significant RT-BOLD relationship across all 50 participants, regardless of age. Second, to eliminate findings that might be driven by particularly strong RT-BOLD relationships in older participants, we then masked out all clusters in which there was an effect of age on RT-BOLD relationships (i.e., the clusters exhibiting a significant age \times

time point interaction with regard to the RT-BOLD relationship as reported in Table 2; in this analysis, we employed a FWE-correction across the entire brain at $p < 0.05$ with an initial height threshold of $p < 0.005$).

A whole brain analysis of regions in which there was a significant RT-BOLD relationship across all 50 participants revealed widespread significant results. Thus, to illustrate the RT-BOLD relationships that we observed, we defined spherical ROIs with a 5 mm radius around the top five peak voxels from the whole brain results, located in left and right insula, left and right inferior parietal cortex, and right medial frontal gyrus (BA 32) (Fig. 2A). RT-BOLD values in each spherical ROI were extracted from each subject. We then mapped the RT-BOLD curves from these ROIs in children/adolescents (≤ 18 years old; $n = 21$) and young adults (as defined in (Carp et al., 2012), ≥ 23 years old; $n = 21$), to provide direct comparisons with prior work (Carp et al., 2012).

3. Results

3.1. Behavioral data

Participants performed the task well (average of mean accuracy across all 6 runs: $94.4\% \pm 4.1\%$). There was no correlation between age and performance as measured by the average of a subject's percentage accuracy over the 6 runs ($r_s = 0.19$, $P = 0.20$). However, compared to males, females were slightly younger ($t(22.969) = 1.72$, $P = 0.10$; Levene's test indicated unequal variances ($F = 4.94$, $P = 0.03$), so degrees of freedom were adjusted from 48 to 22.969) and performed slightly better ($t(21.565) = -1.73$, $P = 0.10$; Levene's test indicated unequal variances ($F = 10.52$, $P = 0.002$), so degrees of freedom were adjusted from 48 to 21.565). Moreover, as expected, mean RT was longer in incongruent ($M = 888.2$ ms, $SD = 145.9$) than congruent ($M = 864.4$ ms, $SD = 138.6$) trials ($t(49) = -8.75$, $P < 0.001$). There were, however, no correlations between age and either mean RT or coefficient of variation of RT across all conditions (congruent and incongruent), or for either condition independently (all $|r_s| < 0.10$, all $P \geq 0.50$). Note that age and IQ were not correlated within the sample (Pearson's $r = 0.09$, $P = 0.54$), and controlling for IQ did not affect the results. See Table 1 for subject means, standard deviations, and ranges for behavioral measures.

3.2. Imaging data

3.2.1. Developmental changes in trial-to-trial RT-BOLD relationships

No interactions involving condition (incongruent, congruent) reached significance in the main RT-BOLD analysis; all significant findings, therefore, are averaged across conditions. Significant age by time point interactions indicated clusters where the RT-BOLD relationship differed with age across the modeled 15-s window (FWE-corrected level of $p < 0.05$ across the entire brain). There were eleven such clusters; these included bilateral clusters in visual cortex/precuneus/cuneus, precentral/postcentral gyrus, inferior frontal gyrus, middle/superior frontal gyrus, and thalamus. These also included unilateral clusters in left inferior parietal lobule and paracentral lobe/cingulate gyrus (Table 2). Scatterplots of RT-BOLD relationship by age across all subjects in each TR in which a significant interaction within these 11 clusters was present are presented in Supplemental Fig. 5. (Graphs of RT-BOLD averaged across all 50 subjects in each of these 11 clusters are presented in Supplemental Fig. 6).

We identified two main patterns of age \times time point interaction among these clusters (i.e., how the RT-BOLD response changed with age). In the first pattern, RT-BOLD became increas-

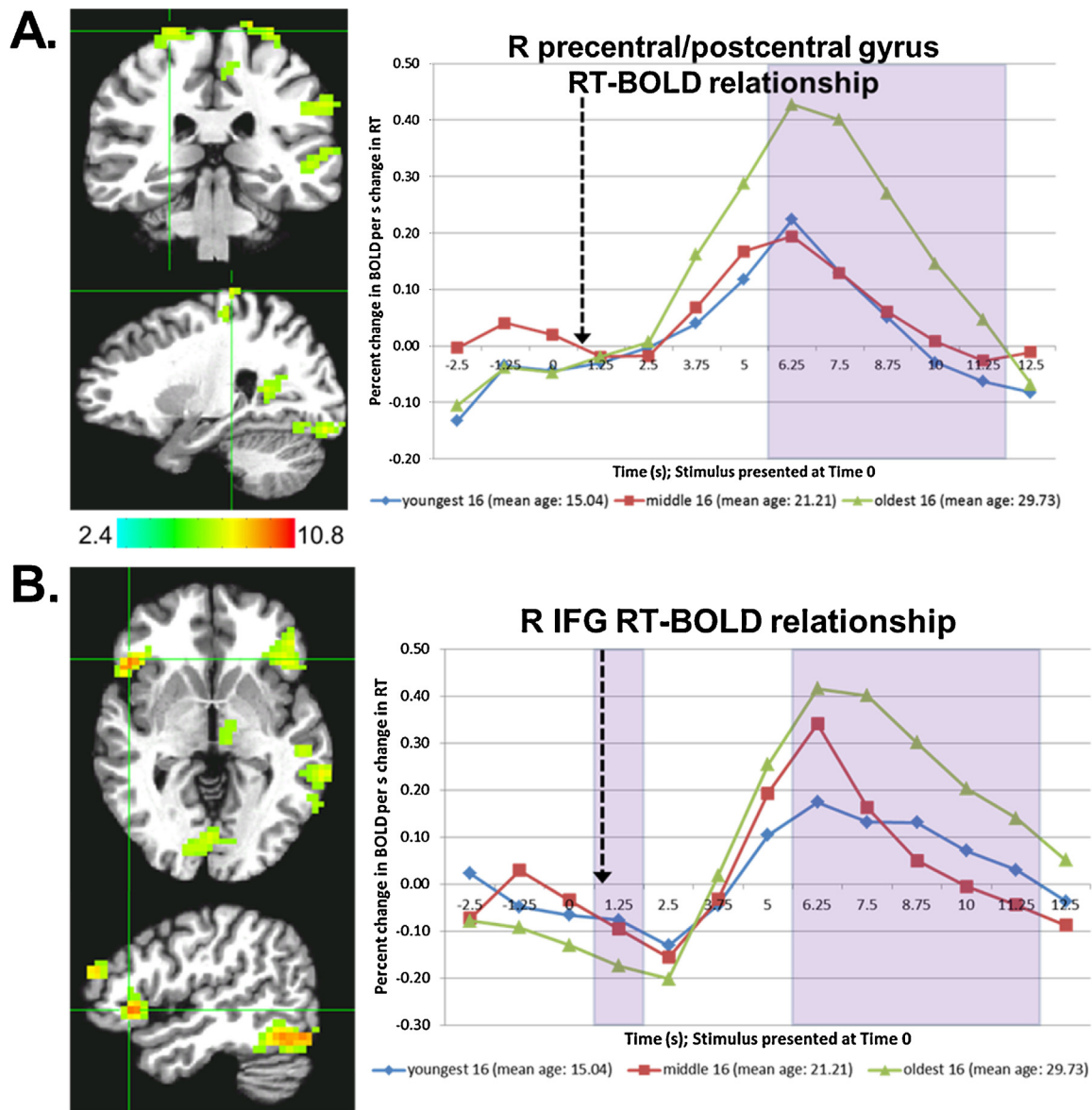


Fig. 1. Representative clusters from the RT-BOLD age \times time point interaction. Sample clusters in which there was a significant age \times time point interaction in the RT-BOLD analysis. Brain slices show F-statistics according to the color bar; only voxels that surpass a height threshold of $P < 0.005$ and are within a cluster of at least 38 voxels (FWE-correction across whole brain at $P < 0.05$) are displayed. In these clusters, there was a developmental difference in the time course of the RT-BOLD relationship (i.e., the relationship between percent change in BOLD response per second increase in mean-standardized reaction time). **A)** Cluster in the right precentral/postcentral gyrus ($k = 58$; crosshairs at peak, coordinates: 23, -29, 69) and representative graph of the RT-BOLD relationship across the cluster in the 16 youngest, 16 middle, and 16 oldest participants. Note that the statistical model included age as a continuous variable. This graph is for illustrative purposes only and is not representative of the analysis, thus no error bars are included. Y-axis represents the percent change in BOLD response per each second change in mean-standardized RT; thus, for example, a positive y-value would indicate an increase in BOLD signal with an increase in mean-standardized RT. Time points at which there was a significant correlation between age and the RT-BOLD relationship (Pearson's correlation; $p < 0.05$) are shaded in purple; the mean RT-BOLD relationship across 21 adults ($\text{age} \geq 23$) was significantly different from 0 (one-sample t -test; $p < 0.05$) at these time points. The dotted line arrow indicates the approximate location within the time window of the group sample mean of correct RT across both conditions (sample mean = 876 ± 142 ms). **B)** Cluster in the right IFG ($k = 58$; crosshairs at peak, coordinates: 47, 24, -1) and representative graph of the RT-BOLD relationship across the cluster in the 16 youngest, 16 middle, and 16 oldest subjects. Note that the statistical model included age as a continuous variable. This graph is for illustrative purposes only and is not representative of the analysis, thus no error bars are included. Y-axis represents the percent change in BOLD response per each second change in mean-standardized RT; accordingly, for example, a positive y-value would indicate an increase in BOLD signal with an increase in mean-standardized RT. Time points at which there was a significant correlation between age and the RT-BOLD relationship (Pearson's correlation; $p < 0.05$) are shaded in purple; the mean RT-BOLD relationship across 21 adults ($\text{age} \geq 23$) was significantly different from 0 (one-sample t -test; $p < 0.05$) at these time points. The dotted line arrow indicates the approximate location within the time window of the group sample mean of correct RT across both conditions (sample mean = 876 ± 142 ms). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ingly positive with age in the later portion of the modeled time window (TR range: 3.75–11.25, most around 6.25; see example in Fig. 1A). This pattern was evident in the following clusters: bilateral occipital/fusiform/precuneus/posterior cingulate, left precentral/postcentral gyrus, left middle/superior frontal gyrus, right precentral/postcentral gyrus, right middle/superior frontal gyrus,

and left paracentral lobule/medial frontal gyrus/cingulate gyrus (clusters 1, 2, 3, 7, 8, and 10 in Table 2). In the other pattern, an increasing positive RT-BOLD response with age was also observed in the later portion of the modeled time window while, additionally, early in the modeled time window (TR range: -2.5–3.75), there was an increasing *negative* RT-BOLD relationship with age (see exam-

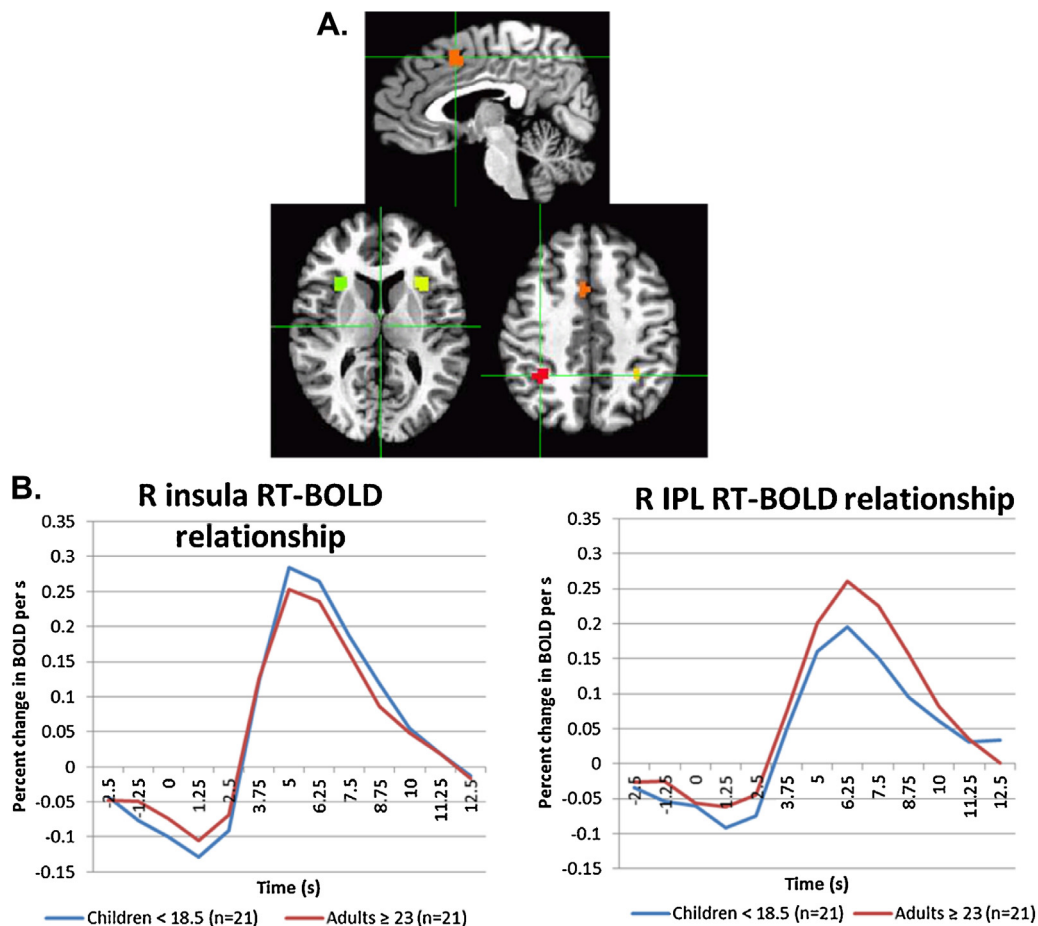


Fig. 2. RT-BOLD relationships are present in children and adolescents. Spherical ROIs were created with a 5 mm radius around the top 5 peak voxels in which we observed a main effect of time point in the RT-BOLD relationship across **all** participants ($n = 50$; $P < 0.005$); regions in which there was an effect of age on RT-BOLD relationships were masked out. **A)** Locations of the five spherical ROIs, each represented by a different color. Clockwise from top: orange: right medial frontal gyrus (5, 10, 45); gold: left inferior parietal lobe (−30, −46, 38); red: right inferior parietal lobule (33, −46, 41); yellow: left insula (−30, 17, 10); green: right insula (30, 17, 10). **B)** Plots of average RT-BOLD curves across child ($n = 21$) and adult ($n = 21$) age groups, as defined by (Carp et al., 2012) in two representative spherical ROIs located in the right insula and right inferior parietal lobule (patterns are similar in all 5 ROIs). Graph axes as in Fig. 1. The RT-BOLD relationship did not differ statistically between groups at any time point (all $P \geq 0.1$).

Table 1
Behavioral results.

	Subject Mean \pm SD	Range Min–Max	Regression slope
Percent Accuracy	94.4 \pm 4.1	81.5 – 98.9	−0.04
Average RT all correct trials (ms)	876.3 \pm 141.9	671.6 – 1330.4	0.93
Average RT correct congruent trials (ms) ^a	864.4 \pm 138.6	657.2 – 1314.5	0.71
Average RT correct incongruent trials (ms) ^a	888.2 \pm 145.9	682.7 – 1346.3	1.15
SD RT all correct trials (ms)	173.5 \pm 65.9	65.5 – 371.6	
SD RT correct congruent trials (ms)	173.9 \pm 66.7	68.2 – 366.4	
SD RT correct incongruent trials (ms)	173.1 \pm 67.0	62.9 – 386.3	
Coefficient of variation of RT all correct trials	0.19 \pm 0.05	0.08 – 0.32	0.001
Coefficient of variation of RT correct congruent trials ^b	0.20 \pm 0.05	0.09 – 0.33	0.001
Coefficient of variation of RT correct incongruent trials ^b	0.19 \pm 0.05	0.08 – 0.31	0.001

^a Subject RT slower on incongruent than congruent trials $P < 0.001$.

^b Coefficient of variation of RT higher for congruent than incongruent trials at trend level ($P = 0.06$).

ple in Fig. 1B). This pattern was evident in clusters in the following regions: left inferior frontal gyrus/superior temporal gyrus, bilateral thalamus, right IFG, left inferior parietal lobule/postcentral gyrus, left middle frontal gyrus (clusters 4, 5, 6, 9, and 11 in Table 2).

Further examination of these clusters revealed that, compared to younger participants, older participants exhibited stronger RT-BOLD relationships in several brain regions (see Fig. 1 for examples from two clusters). The nature of this developmental difference was twofold. In clusters exhibiting the first pattern, in which RT-BOLD became increasingly positive with age in the later portion

of the modeled time window (closer to the time of the peak BOLD response), older participants exhibited a more positive RT-BOLD relationship than younger participants (Fig. 1A). In clusters exhibiting the second pattern, this increase in positive RT-BOLD response with age later in the modeled window was still evident, but RT-BOLD association became more *negative* with age early in the modeled event window (i.e., before the peak of the BOLD response): specifically, older participants exhibited a more negative RT-BOLD relationship than younger participants (Fig. 1B; green line represents 16 oldest participants). Negative RT-BOLD associa-

Table 2
fMRI results for RT-BOLD analysis.

Cluster Region (Brodmann Area)	No. voxels in cluster	Talairach Coords Cluster Peak x y z			Cluster Peak F-statistic
<i>Age by time point interaction</i>					
Bilateral occipital cortex, fusiform, lingual gyrus, cuneus/precuneus, posterior cingulate	1004	40	−74	−15	10.82
L precentral/postcentral gyrus (4/3/6)	216	−40	−18	62	6.92
L MFG/SFG (10/9/46)	144	−44	31	27	5.65
L IFG/STG (47/38/45)	111	−40	17	−11	8.11
Bilateral thalamus	90	12	−11	10	3.74
R IFG (47/45)	58	47	24	−1	8.40
R precentral/postcentral gyrus (4/3)	58	23	−29	69	4.63
R MFG/SFG (10/46)	55	47	41	20	6.15
L IPL/postcentral gyrus (40/2)	48	−58	−25	31	4.67
L paracentral lobule/medial frontal gyrus/cingulate gyrus (6/31)	48	−12	−22	55	3.69
L MFG (6)	48	−30	−1	48	4.50

Note: L = left; R = right; MFG = Middle Frontal Gyrus; IFG = Inferior Frontal Gyrus; STG = Superior Temporal Gyrus; IPL = Inferior Parietal Lobule.

tions indicate less activation on trials with relatively slow RTs than on trials with relatively fast RTs. Positive RT-BOLD associations indicate more activation on trials with relatively slow RTs than on trials with relatively fast RTs. The age-related increases of negative RT-BOLD relationships early in the modeled window and/or positive RT-BOLD relationships late in the modeled window were evident in all 11 significant clusters. However, both the timing of the effects (e.g., compare the timing of the early effect in Fig. 1A to B) and the significance of the simple effects varied across clusters.

3.2.2. RT-BOLD relationships are present in children and adolescents

We observed strong, widely-distributed RT-BOLD associations at **all** ages. In many regions, these strong RT-BOLD relationships in children and adolescents did not differ from those of the young adults. RT-BOLD responses of children and adolescents ($n = 21$) extracted from spherical ROIs drawn around the top five peak voxels in left and right insula, left and right inferior parietal cortex, and right medial frontal gyrus (Fig. 2A) did not differ in these regions from those of the young adults ($n = 21$; for representative graphs see Fig. 2B). Moreover, in all 5 spherical ROIs, there were ≥ 8 TRs (out of 13) at which the RT-BOLD relationship in the child/adolescent group was significantly different than zero (all $P < 0.05$).

4. Discussion

This study is important because it is the first to examine the development of the brain-behavior relationship on a trial-by-trial basis as a function of age. We observed strong RT-BOLD relationships in many brain regions, including fronto-parietal association cortex and thalamus, all of which manifested more powerfully with age. These RT-BOLD associations may provide a useful cross-task tool for elucidating brain-behavior associations across development and pathological states. Below we discuss these findings, and their relevance to the broader literature, in greater detail.

4.1. Age-related differences in trial-to-trial RT-BOLD relationships

The strongest RT-BOLD associations were evident in the oldest participants. The data therefore suggest that these relationships develop throughout childhood and adolescence. Notably, the increase in the strength of RT-BOLD relationships was not limited to the time of the peak response (Carp et al., 2012) or to positive relationships between RT and the BOLD signal (i.e., regions in which the BOLD signal increases with RT) (Kim et al., 2013). Rather, such age-related variation manifested both early and late in the mod-

eled window. In addition, condition did not influence the model in this RT-BOLD analysis, indicating that task difficulty did not affect the age by time point interaction of the RT-BOLD relationship. Further, while RT-BOLD relationships became stronger with age, they could still be detected in early adolescence, unlike in some prior research (Carp et al., 2012). Finally, while robust RT-BOLD relationships were found at all ages, our data suggest that development involves region-specific changes in these relationships.

4.2. Neural regions exhibiting age-related RT-BOLD relationship differences

Several global-local tasks with stimuli similar to those used in the present study have been used to study selective attention. These studies have identified task-related responses in similar regions to those showing developmental RT-BOLD relationships here, including frontal areas, precentral gyrus, inferior parietal lobe, thalamus, and visual regions such as the precuneus and fusiform (Weissman et al., 2002). Other methodologies also support the role of these regions in the performance of a global-local selective attention task: e.g., “virtual lesions” of the intraparietal sulcus (IPS) with TMS stimulation disrupt performance of a global Navon task (i.e., identification of the global letter) (Whitney et al., 2012), and TMS stimulation of the right intraparietal sulcus at different frequencies differentially affects global and local processing (Romei et al., 2011). Notably, in the present study, no age-related differences were identified in the anterior cingulate cortex, a region that is often identified in similar tasks and has been proposed to detect task-related response conflict (Weissman et al., 2002, 2003, 2009; Lux et al., 2004). It is important to note, however, that no interactions involving condition (incongruent, congruent) reached significance in the main RT-BOLD analysis and therefore, all significant findings are averaged across conditions. Thus, there were no developmental results specific to conflict (i.e., incongruent versus congruent stimuli).

The regions identified as showing age-dependent variation in RT-BOLD relationships include several core attention network areas. These regions constitute components of both the dorsal and ventral attention networks, and have been shown to be active in adults during attentional tasks and have been strongly implicated in RT-variability in prior studies with adults (e.g., Weissman et al., 2006). In addition, the strong results in visual processing regions are consistent with the biased competition model of visual attention (Desimone, 1998), in which top-down regions amplify the response of task- and/or goal-relevant perceptual processing areas. Age-related differences in RT-BOLD identified in these dorsal, ventral,

and visual regions are likely related to developmental changes in attention processes. Interestingly, a recent resting state analysis in a dichotomous sample (i.e., children versus adults) found an asymmetric pattern of development in the two attentional networks (dorsal and ventral) as measured by intrinsic connectivity (Farrant and Uddin, 2015). In this study, the authors found between-group differences in functional connectivity between dorsal and ventral attention network ROI seeds and several regions identified in our main analysis, including the left postcentral gyrus, bilateral posterior cingulate gyrus, and left thalamus.

4.3. Relevance of the present findings to prior work

The current study maps precisely the chronometry of brain-behavior relationships that correspond to RT variations, reporting significant age differences in the strength of such brain-behavior relationships. Our methods allowed us to model brain-behavior relationships in children and adolescents with greater temporal precision than prior work (Carp et al., 2012; Kim et al., 2013). Specifically, our statistical techniques parsed brain-behavior associations on a trial-by-trial basis, facilitated by an approach to data acquisition and analysis that allowed modeling of fluctuating brain-behavior associations *within* a trial. Thus, these methods charted the precisely orchestrated chronometry of healthy brain-network deployment during, and in response to, an individual's reaction to a stimulus.

These methods also revealed the subtle ways in which brain-behavior relationships differ between children/adolescents and adults. Such subtleties can be obscured unless brain-behavior associations are probed with considerable temporal precision. In particular, the use of standard fMRI analysis techniques, which impose a standard HRF function and average BOLD responses to large, diverse stimuli, have only identified differences between children and adults during the peak of the BOLD response (Carp et al., 2012). Here, using a FIR model and trial-by-trial modulation analysis, we added to this literature by showing that the immature RT-BOLD relationship differs from the adult one at both early and late time points within a trial. As such, these findings add to a prior cross-sectional study of developmental differences in the RT-BOLD relationship (Carp et al., 2012) by showing that such developmental differences also occur in the early time period of a BOLD time course, not just at the peak of the BOLD response. Importantly, this age-related pattern is more complex than simply becoming “more positive” with age, showing increased negative *and* positive RT-BOLD associations distributed across the modeled time window. Notably, the “early negative” and “late positive” RT-BOLD relationships in older participants resemble those previously reported in a similarly aged group of adults (Weissman et al., 2006). These findings help to specify neural differences across the course of development associated with ISVRT, but the precise interpretation of the relationship between differences in the early and late epochs and changes in ISVRT require further work.

4.4. Psychological processes underlying variation in RT

Variation in RT has been hypothesized to reflect several different psychological processes including attention regulation, sustained attention, the detection of response conflict, effort, and arousal (Li et al., 2009; Gomez-Guerrero et al., 2011; Bora et al., 2006; Weissman et al., 2006; Prado and Weissman, 2011; Chee et al., 2008; Whyte et al., 1995). It is also important to note that several studies have shown a relationship between time spent on task and activation, particularly in the posterior/dorsal medial frontal cortex (Grinband et al., 2011; Weissman and Carp, 2013). However, in the current sample, there was no relationship between age and mean RT, nor were there any interactions between age, mean

RT, and time point in any of the 11 clusters identified in the age \times time interaction. Because ISVRT typically decreases over development (Williams et al., 2005, 2007; Dykiert et al., 2012; Li et al., 2009, 2004; Tamnes et al., 2012), and the developmental differences in RT-BOLD relationships that we observed were located in executive control, regulatory, and attention network regions, we speculate that ISVRT likely relates to attention modulation, consistent with the view that trials with slow RT represent lapses of attention (Weissman et al., 2006). Critically, our findings indicate that, relative to older individuals, younger individuals exhibit a reduction of both early, negative *and* late, positive RT-BOLD effects. This result may indicate that the attention systems of the adolescent brain remain immature relative to those of the adult brain. Decreased activation in control regions along with a more diffuse pattern of activation during attentional tasks in children, compared to adults, has been reported previously (Konrad et al., 2005). Several researchers have suggested that maturation across childhood and adolescence is associated with qualitative differences in processes underlying executive functions (Luna et al., 2004). Neurodevelopmental changes associated with maturation that result in qualitative differences in function may include increases in 1) focalization of networks (Konrad et al., 2005), 2) long-range connections that support top-down modulation (Luna et al., 2010), 3) top-down effective connectivity (Hwang et al., 2010), and 4) synaptic connectivity (Edin et al., 2007). Luna and colleagues (Luna et al., 2010) have noted that developmental qualitative differences in neural function might be best observed through a comparison of the BOLD time courses, as differences in BOLD response, representative of qualitative differences, might be obscured in standard group analyses. The FIR methods employed in the present study identify such developmental differences precisely by comparing the time course of the RT-BOLD relationship. Alternatively, it is possible that a different paradigm is needed to explore RT-BOLD relationships more thoroughly in children, as this task and paradigm were originally designed for use in adults. This alternative, though conceivable, is less likely because we did observe regions in which there were equally robust RT-BOLD relationships in all subjects.

One potential explanation for the current results could be an age-related shift in the latency of the peak BOLD response. However, the pattern of the findings did not support this possibility as age-related differences in the mean BOLD response generally reflected reductions in peak magnitude of the response (as shown in Supplemental Figs. 7 and 8), rather than an age-related shift in magnitude. Moreover, the average BOLD response and the BOLD-RT correlation analyses generally revealed different brain regions. The presence of latency differences in peak responses would be expected to generate overlapping clusters for average BOLD response and BOLD-RT correlations analyses.

In spite of the observation of age-related differences in neural function, we did not detect any age-related variation in ISVRT in our participant sample. While the reasons for this null finding remain unclear, several fMRI studies have not found significant between-subject behavioral differences inside the scanner on tasks that elicit behavioral differences outside of the scanner (McClure et al., 2007; Fani et al., 2012; Monk et al., 2008; Solomon et al., 2015; Finger et al., 2008). All of these studies, however, do identify between-subject neural differences despite the lack of behavioral differences. Moreover, age-related differences in behavior are sometimes smaller than age-related differences in brain function (Deeley et al., 2008). Thus, methodological and statistical factors may explain the lack of an age effect in ISVRT. Despite the lack of age-related variation in ISVRT in the current sample, decreases in ISVRT from childhood through young adulthood have been demonstrated consistently in behavioral studies across several task paradigms (Williams et al., 2005, 2007; Dykiert et al., 2012; Li et al., 2009, 2004; Tamnes et al., 2012), paralleling the normal developmental pattern of

both executive functions (Waber et al., 2007) and structural brain development (Giedd, 2004; Gogtay et al., 2004). Future studies employing more difficult or effortful tasks, and/or larger samples, might better reveal age-related decreases in ISVRT.

Our findings suggest that there are, in fact, age-related neural differences related to trial-by-trial variation in RT, regardless of whether behavioral differences are measurable. In fact, the lack of age-related differences in RT suggests that the results of the present study are likely to reflect variation-related neural differences with age and not spurious findings resulting from reaction time latency differences. Thus, we think that the present findings are important in elucidating differences in neural response with age.

5. Conclusions: understanding development of RT-BOLD relationship may help elucidate normal and abnormal brain development

In addition to potentially serving as a measure of brain-behavior associations related to attentional regulatory processing, the RT-BOLD relationship, both early and late in the BOLD response, may reflect brain development related to executive functioning. The results of this and future studies of the phenomenon may be of particular use in understanding disorders associated with abnormal development of executive functions, such as ADHD (Shaw et al., 2007, 2012). On a related front, increased ISVRT has also been associated with many developmental neurological and psychiatric disorders (Bora et al., 2006; Leth-Steensen et al., 2000; Kaiser et al., 2008; Brotman et al., 2009; Castellanos et al., 2005; Epstein et al., 2011), and has even been observed in healthy people at increased familial risk for such disorders (i.e., first-degree relatives: Adleman et al., 2014; Brotman et al., 2009; Nigg et al., 2004; Bidwell et al., 2007). Therefore, understanding the brain mechanisms underlying ISVRT (i.e., RT-BOLD associations), is an important next step for the field. By beginning to delineate the healthy development of RT-BOLD associations throughout the brain, the present study has helped lay the groundwork for future research in psychopathological populations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.dcn.2016.05.001>.

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